24. Brevetti G, Schiano V, Chiariello M. Endothelial dysfunction: a key to the pathophysiology and natural history of peripheral arterial disease? Atherosclerosis 2008;197:1-11.
25. Kwon HR, Min KW, Ahn HJ, Seok HG, Lee JH, Park GS, et al. Effects of aerobic exercise vs. resistance training on endothelial function in women with type 2 diabetes mellitus. Diabetes Metab J 2011;35:364-73.
26. Ades PA, Savage PD, Lischke S, Toth MJ, Harvey-Berino J, Bunn JY, et al. The effect of weight loss and exercise training on flow-mediated dilatation in coronary heart disease: a randomized trial. Chest 2011;140:1420-7.
27. Mika P, Konik A, Januszek R, Petriczek T, Mika A, Nowobilski R, et al. Comparison of two treadmill training programs on walking ability and endothelial function in intermittent claudication. Int J Cardiol 2013;168:838-42.
28. Gresele P, Migliacci R, Arosio E, Bonizzoni E, Minuz P, Violi F, et al. Effect on walking distance and atherosclerosis progression of a nitric oxide-donating agent in intermittent claudication. J Vasc Surg 2012;56:1622-8. 28 e1-5.
29. Kenjale AA, Ham KL, Stabler T, Robbins JL, Johnson JL, Vanbruggen M, et al. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. J Appl Physiol 2011;110:1582-91.
30. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on haemodynamics in intermittent claudication: a systematic review of randomized controlled trials. Sports Med 2010;40:433-47.
31. Vogt MT, McKenna M, Anderson SJ, Wolfson SK, Kuller LH. The relationship between ankle-arm index and mortality in older men and women. J Am Geriatr Soc 1993;41:523-30.
32. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1999;19:538-45.
33. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. Atherosclerosis 1991;87:119-28.
34. Diehm C, Lange S, Darius H, Pittrow D, von Stritzky B, Tepohl G, et al. Association of low ankle brachial index with high mortality in primary care. Eur Heart J 2006;27:1743-9.
35. Brevetti G, Silvestro A, Di Giacomo S, Bucur R, Di Donato A, Schiano V, et al. Endothelial dysfunction in peripheral arterial disease is related to increase in plasma markers of inflammation and severity of peripheral circulatory impairment but not to classic risk factors and atherosclerotic burden. J Vasc Surg 2003;38:374-9.
36. Silvestro A, Scopacasa F, Ruocco A, Oliva G, Schiano V, Zincarelli C, et al. Inflammatory status and endothelial function in asymptomatic and symptomatic peripheral arterial disease. Vasc Med (London, England) 2003;8:225-32.
37. Lind L. Arterial stiffness but not endothelium-dependent vasodilation, is related to a low ankle-brachial index in the elderly—The Prospective Investigation of the Vasculature in the Uppsala Seniors (PIVUS) Study. Open Atheroscler Thromb J 2008;I:1-5.
38. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453-61.
39. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002;136:873-83.
40. McPhail IR, Spittell PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol 2001;37:1381-5.
41. Garber CE, Monteiro R, Patterson RB, Braun CM, Lamont LS. A comparison of treadmill and arm-leg ergometry exercise testing for assessing exercise capacity in patients with peripheral arterial disease. J Cardiopulm Rehabil 2006;26:297-303.
42. Ahimastos AA, Walker PJ, Askew C, Leicht A, Pappas E, Blombery P, et al. Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial. JAMA 2013;309:453-60.
43. Stevens JW, Simpson E, Harnan S, Squires H, Meng Y, Thomas S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. Br J Surg 2012;99:1630-8.
44. Siasos G, Tousoulis D, Oikonomou E, Zaromitidou M, Verveniotis A, Plastiras A, et al. Effects of omega-3 fatty acids on endothelial function, arterial wall properties, inflammatory and fibrinolytic status in smokers: a cross over study. Int J Cardiol 2013;166:340-6.
45. Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. Circulation 2011;123:87-97.
46. Izquierdo-Porrera AM, Gardner AW, Powell CC, Katzel LI. Effects of exercise rehabilitation on cardiovascular risk factors in older patients with peripheral arterial occlusive disease. J Vasc Surg 2000;31:670-7.
47. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. JAMA 2009;301:165-74.
48. Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. J Vasc Surg 2005;42:1122-30.
49. Munzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. Ann Med 2008;40:180-96.
50. Neunteufl T, Heher S, Kostner K, Mitulovic G, Lehr S, Khoschsorur G, et al. Contribution of nicotine to acute endothelial dysfunction in long-term smokers. J Am Coll Cardiol 2002;39:251-6.

Submitted Sep 11, 2013; accepted Oct 17, 2013.

DISCUSSION

Dr Larry Kraiss (*Salt Lake City, Utah*). Congratulations to Ms Chong who very ably presented this paper. I also thank the authors for a timely submission of their paper for my review.

The UCSF group is to be commended for reminding us that PAD is in reality a systemic disease. They report that self-reported walking impairment correlates best with objectively measured endothelial function, which is a systemic condition as opposed to the ABI, which might be considered a limb-specific condition. Walking impairment is an endpoint that is sensitive to many factors, only one of which is the ABI or the degree of hemodynamic impairment that the limb experiences. Also, I think we have all had patients who underwent intervention for claudication with an improvement in ABI but a disappointing response in walking distance. So, this particular conclusion, on its face, is not too difficult to accept, but I do have some reservations about the data supporting this conclusion.

First, although the study population is extensively phenotyped in terms of endothelial function, ABI, and multiple biochemical parameters, the clinical characterization is suboptimal. As we have heard before during this meeting, the venerable Rutherford classification has probably outlived its usefulness, so I question the accuracy of self-reported walking distance in terms of "blocks." There is no information about whether these self-reported outcomes are accurate or reproducible. Your study would be greatly strengthened by an objective measure of walking impairment, such as the 6-minute walk test. While the authors acknowledge this limitation, it remains a major drawback to the study's impact.

Ms Karen Chong. We acknowledge this as a limitation of our study. We are therefore excited to launch our trial that will have a 6-minute walk test as an outcome in addition to self-reported Rutherford and the WIQ.

Dr Kraiss. Second, the authors report that endothelial function as measured by brachial artery FMD is the only parameter that correlates with severity of claudication classified by Rutherford category. However, in the manuscript, there is a 100% overlap between endothelial function scores for group II compared to group III. This challenges my statistical "smell" test.

Finally, the authors report that endothelial function did not correlate with ABI but the *P* value for this relationship is .21. So, there is an 80% chance that ABI and endothelial function really do correlate. Since there are so few subjects in the Rutherford class I and II categories, I wonder if it is really true that ABI and endothelial function do not correlate or whether this is in essence a type II error.

These are issues that I will let the authors address in the JVS editorial process, as I am not sure that a discussion around these points will be all that informative this morning. I do have four straightforward questions for the authors:

1. How were patients selected for the study? Were they consecutive? Were they new or established patients, or both?
2. Did inflow or outflow location of disease correlate with endothelial function?
3. Had any patients in the study received previous treatment directed at claudication?
4. Have any of the study patients subsequently received treatment for claudication? If so, did endothelial function predict treatment outcome?

This is a worthwhile area of study and I encourage the authors to continue their investigations. I suspect that they are on to something that may ultimately help us better select claudicants who will benefit the most from intervention.

Ms Chong. To answer your questions:

1. We essentially attempted to recruit any patient that came through our clinic with PAD, provided that they fit our eligibility criteria and provided consent. This included both new and established patients.
2. We have not yet looked at the location of the disease, but that is actually the next direction for us. We plan to look at angiographic or MR imaging to determine location of lesions and quantity of collaterals to see if these factors might correlate with endothelial function or walking disability.
3. There were patients that had prior revascularization, but this was the minority. In those cases, we based our clinical Rutherford category on their symptoms prior to any revascularization to ensure that their native symptoms would be captured.
4. Study patients certainly have subsequently received treatment for claudication. However, we have not collected these data, but we do have access to it. It would be interesting to see if endothelial function does predict treatment outcome. For now, our lab, the Vascular Integrated Physiology and Experimental Therapeutics Lab (VIPERx), is focusing on establishing a modifiable risk factor in patients with claudication.